Application No.: 10/070,277
Inventor: EHRHARDT et al.
Reply to Office Action of 23 February 2006
Docket No.: 50716

REMARKS/ARGUMENTS

Claims 1-21 are pending. Claims 21-23 are new.

Rejection under 35 USC §112 ¶1

Claims 9-10, 14 and 19-20 stand rejected as allegedly non-enabled. Applicants respectfully disagree.

Regarding the enablement requirement of §112, the Federal Circuit has held that "[t]he specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they a ready know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation'" (*Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. (2003)).

Applicants respectfully reassert the arguments of record and that the claims are fully enabled by the specification of the application in combination with the general knowledge of one of ordinary skill in the art.

Applicants have provided specific guidance for the enablement of claims 9 and 14. The Examiner is directed to Example 2 of the specification for recitation of comparisons of percentage identity of the protein of SEQ ID NO: 1 and various other functional dihydroorotases. More specifically, the protein encoded by SEQ ID NO: 1 has 78% identity with *Arabidopsis thaliana* dihydroorotase, 58% identity with *Synechocystis* dihydroorotase, and 55% identity with *E. coli* and *Pseudomonas putida* dihydroorotase. The above mentioned data is supplemented by the Genbank accession numbers listed on page 2 of the specification and by any other dihydroorotase sequence known at the time of filing. Indeed, any reference known to one of ordinary skill in the art is allowed to show enablement. The Federal Circuit recently stated in *Falkner v. Inglis*, that "[a] patent need not teach, and preferably omits, what is well known in the art." (448 F.3d 1357, 1365 (Fed. Cir. 2006)(quoting *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)). *Falkner* acknowledges the coming of age of molecular biology by asserting that a chemical structure required for a claim does not always have to be provided by a specification and in the application. Possession of such details can be imputed if

shown in a publication before the filing date which, for example, is exemplified in this application by Zhou et al., Plant Physiol. 114: 1569 (1997). Accordingly, Applicants recitation of DNA sequence of SEQ ID NO: 1 or a DNA sequence having a homology of at least 60% with respect to SEQ ID NO: 1 and which encodes a protein which has the enzymatic activity of a dihydroorotase is enabled by the disclosure of the invention and the knowledge of one of ordinary skill in the art.

The Examiner asserts, using the standard USPTO biotechnology rejection language, that the specification does not "reasonably provide enablement" for the recited claims. As stated above, the specification does provide the necessary guidance to one of ordinary skill in the art to practice the claimed invention. Moreover, as stated in MPEP 2164.04, quoting *In re Marzocchi*,

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement (439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)(emphasis in original)).

The Examiner has failed to provide objective evidence that "there is reason to doubt the objective truth of the statements" of Applicants' specification (439 F.2d at 223). If, contrary to Applicants' assertions that the invention is enabled, the Examiner has used information from examples not of record, Applicants respectfully request an Examiner's affidavit indicating the use of personal knowledge and allowance for Applicants to respond to the personal knowledge.

Further, the Examiner asserts that "it is not routine in the art to screen for multiple substitutions or multiple modifications" (23 February 2006 Office Action, page 3). Applicants respectfully assert that not only is screening for multiple substitutions or multiple modifications routine, but that the Examiner need only look to the USPTO itself for references. The numerous Affymetrix patents clearly show that large scale screening was and is state of the art and that a comparison of a sufficient number of sequences of dihydroorotase to the disclosed dihydroorotase can be performed; no undue experimentation would be required. Moreover, using the search function on the Affymetrix website (https://www.affymetrix.com/index.affx), 1052 references (first page attached hereto), from 1990-2002, related to screening were found

providing additional objective evidence of the routine nature of the screening.

Additionally, one of ordinary skill in the art can easily obtain mutations based on already known sequences such as SEQ ID NO: 1. Applicants respectfully assert that screening for mutant enzymes is routine for the skilled artisan and can be done, e.g. by *in vivo* mutagenesis, which is based on the use of *E. coli* strains having mutations in the genes for the DNA repair system (e.g. mutHLS, mutD, and mutt, *see* e.g. Rupp, W.D. (1996)). The use of this technique is illustrated in Greener et al. (1994). In this regard, the Examiner has repeatedly misinterpreted Greener at al., providing the same incorrect analysis in the Actions of the following dates: 1) 21 September 2005; 2) 19 January 2006; and 3) 23 February 2006. The Examiner asserts the same sentence in all three Actions stating:

> The reference of Greener has limited use and does not teach the applicability to any gene, is time consuming and expensive and only limited number of random mutants can be generated (*see* page 32, column 1-2) as against modifying a sequence (SEQ ID NO: 1) by 40%

In repeating the aforementioned, the Examiner asserts in the Office Action of 23 February 2006 that "Applicants' new arguments are a newer version of the old argument and are considered no different..." Applicants respectfully assert that any repetition of "old argument[s]" is because of the incorrect analysis of Greener et al. The Examiner is directed to page 32, bottom of column 1 to the top of column 2, of Greener et al. wherein the art reference recites, when describing the problems with PCR, the following:

> First, the gene of interest must be recloned into a vector after the PCR reaction. Second, because of the clonal expansion during the PCR amplification reaction, to guarantee that independent mutations have been generated, individual reactions should be performed. **This makes the method very time-consuming and expensive, and only a limited number of random mutants can be generated.** (emphasis added)

The Examiner is further directed to Greener et al. page 33, top of column 2, wherein the reference states the following:

> Protein Engineering Using XL-Red Mutator Strain
> The major advantage of performing random mutagenesis in XL1-Red is its efficacy when there is no selectable/screenable phenotype of the gene of interest.

However, if there is a genetic screen to monitor mutations, the mutator strain makes it very easy to isolate mutants of interest.

Accordingly, Applicants respectfully assert that mutator strains such as XL1-Red have a high mutation rate, and are extremely easy and cost effective to handle. Plasmids of XL1-Red can be isolated easily (e.g. by commercially available isolation kits in a very short period of lime) and transferred into *E. coli* strains for recombinant expression (e.g. in multiple well plates to enable a large number of clones to be analyzed). Simple tests for functionality (*See e.g.*, those disclosed in the specification in Example 11) in high throughput methods easily lead to a large number of functionally equivalent mutants of dihydroorotase. These functionally equivalent mutants can be used for the method of the claimed invention. Consequently, one of ordinary skill in the art can readily obtain dihydroorotase sequences, using a DNA sequence of SEQ ID NO: 1 or a DNA sequence having a homology of at least 60% with respect to SEQ ID NO: 1 and which encodes a protein which has the enzymatic activity of a dihydroorotase.

Additionally, Applicants respectfully assert that the procedures related to PCR methodology, as described in Greener et al., have no bearing on the ability of one of ordinary skill in the art to practice the instant invention. Therefore, Greener et al. fails to teach against generating, in a first step, dihydroorotase using a DNA sequence of SEQ ID NO: 1 or a DNA sequence having a homology of at least 60% with respect to SEQ ID NO: 1 and which encodes a protein which has the enzymatic activity of a dihydroorotase as suggested by the Examiner.

Further still, the Examiner makes assertions regarding substituting amino acids, the predictability of results and obtaining the desired activity in the end product. Applicants respectfully assert that one of ordinary skill in the art would be able to determine, to a sufficient degree, as to not require undue experimentation, amino acid substitutions. First, a skilled artisan would know that in certain positions, certain amino acid changes would render the subsequent protein inactive and would avoid using the substitutions. MPEP 2164.08(b) states that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled." Thus, Applicants respectfully assert that even if the skilled artisan substituted an amino acid at a non-optimum position, the invention is still enabled. Second,

computational techniques were available at the time of filing for protein structural predictions based on sequence listings. The Examiner is directed to, for example, the Boston University Protein Sequence Analysis server (available at http://bmerc-www.bu.edu/psa/), which has been available since at least the filing date of this application. Consequently, modification of the claimed sequence in regards to the claims, would have been sufficiently routine to one of ordinary skill in the art.

In this regard, The Examiner has provided no evidence to support the assertions of undue experimentation. The Examiner asserts on page 4 of the 23 February 2006 Office Action that "the experimentation left to those skilled in art is unnecessarily, and improperly, extensive and undue." Applicants respectfully disagree. In order to establish a *prima facie* rejection, the Examiner must provide evidence of the necessity of the "undue experimentation." Along these lines, the Examiner has not stated why one skilled in the art could not supply the allegedly needed enabling information without undue experimentation. If the Examiner has personal knowledge regarding experimentation volume, Applicants respectfully request submission of an Examiner's affidavit and thereafter be provided a full and fair opportunity to respond. In the absence of such evidence or an affidavit, Applicants respectfully request that this rejection be withdrawn. Moreover, merely because experimentation may be "difficult and time consuming," the Federal Circuit fails to demand that the experimentation stand rejected as undue (*Falkner v. Inglis*, 448 F.3d 1357, (Fed. Cir. 2006) (quoting from the Board of Patent Appeals and Interferences decision on appeal).

In sum, Applicants respectfully assert that the instant claims are enabled based upon the requirements of §112, the MPEP and the rulings handed down from the Federal Circuit. One of ordinary skill in the art would have been able to practice the instant invention without undue experimentation based on a combination of the contents of the instant Specification when analyzed by the skill in the art at the time of filing. Accordingly, Applicants respectfully request withdrawal of the instant enablement rejection and favorable action is solicited.

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Rejection under 35 USC 112 ¶2

Applicants respectfully assert that this rejection is moot in light of Applicants amendments in accordance with the Examiner's instructions. The term "of" has been added to claim 14 and the term "substrate" has been replaced with the tern "substance" also in claim 14. Accordingly, Applicants respectfully request withdrawal of the 112 ¶2 rejection.

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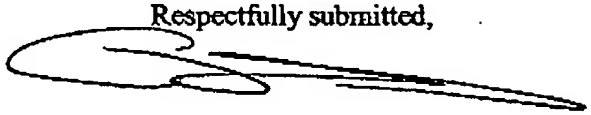
Conclusion

Applicants respectfully submit that the present application is in condition for allowance, which action is courteously requested. Please charge the two-month extension fee to the credit card listed on the enclosed Form PTO-2038. Please charge any shortage in fees due in connection with the filing of this paper to Deposit Account 14.1437. Please credit any excess fees to such account.

Respectfully submitted,



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APPENDIX

This appendix includes attached sheets as specified in the **REMARKS/ARGUMENTS** for consideration by the Examiner.

AFFYMETRIX

- -> Scientific Publications
  - -> Advanced Search
  - -> Full List
  - -> Foundational Publications
- -> Academic Center
- -> Research Highlights
- -> Consortia Program
- -> Affymetrix Research
- -> Affymetrix Newsletter
- -> Standards Program

Refine Search | New Search

Results

1052 publications found using terms:

From: 1990
Through: 2002

Printer-friendly list

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2002 (589) | 2001 (239) | 2000 (104) | 1999 (52) | 1998 (31)
1997 (9) | 1996 (11) | 1995 (2) | 1994 (6) | 1993 (5)
1992 (2) | 1991 (2)

2002 PUBLICATIONS

-> Understanding cancer through gene expression profiling
Aburatani, H. International Congress Series 1246, 261-270, 2002

-> Osteopontin identified as lead marker of colon cancer progression, using pooled sample expression profiling
Agrawal, D. *et al.* Journal of the National Cancer Institute 94(7), 513-21, 2002 PubMed

-> Projection of an immunological self shadow within the thymus by the aire protein
Anderson, M. S. *et al.* Science 298(5597), 1395-401, 2002 PubMed

-> Molecular techniques for studying gene expression in carcinogenesis
Ahmed, F. E. Journal of Environmental Science and Health. Part C: Environmental Health Sciences 20(2), 77-116, 2002 PubMed

-> Changes in cervical keratinocyte gene expression associated with integration of human papillomavirus 16
Alazawi, W. *et al.* Cancer Research 62(23), 6959-65, 2002 PubMed

-> Microarray studies of gene expression in circulating leukocytes in kidney diseases
Alcorta, D. *et al.* Experimental Nephrology 10(2), 139-49, 2002 PubMed

-> Odontogenic carcinoma: a functional genomic comparison with oral mucosal squamous cell carcinoma
Alevizos, I. *et al.* Oral Oncology 38(5), 504-7, 2002 PubMed

-> MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia
Armstrong, S. A. *et al.* Nature Genetics 30(1), 41-7, 2002 PubMed

-> "A system biology" approach to bioinformatics and functional genomics in complex human diseases: arthritis
Attur, M. G. *et al.* Current Issues in Molecular Biology 4(4), 129-46, 2002 PubMed

-> How microarrays can improve our understanding of immune responses and vaccine development
Aujame, L. *et al.* Annals of the New York Academy of Sciences 975, 1-23, 2002 PubMed

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